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Research article

Analysis of immunological and biochemical parameters after booster dose vaccination using protein-based and inactivated virus vaccine for safety

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ABSTRACT

Introduction: Heterologous vaccines enhance the immune response to new variants and allow flexibility in booster administration when the original vaccine is unavailable. Studies show that heterologous boosters can generate comparable or superior antibody responses compared to homologous boosters. Considering rare side effects is essential in evaluating COVID-19 vaccines, especially those associated with ChAdOx1-S (AstraZeneca) and Ad26.COV2.S (Janssen), including blood clotting and idiopathic thrombocytopenia. Severe side effects, such as myocarditis and pericarditis, may occur after Pfizer or Moderna boosters but are rare.

Methods: This study administered two vaccines: the Sinopharm inactivated virus vaccine and the Razi-CoV-Pars (RCP) booster. Various evaluations included biochemical markers, coagulation factors, autoimmune antibodies, and antibodies against concerning variants.

Results: All 90 participants exhibited a notable rise in antibody levels against the variant of concern (VOC). Participants receiving the Razi-CoV-Pars booster after Sinopharm/BBIBP-CorV showed significantly higher antibody levels (Wuhan ~ 3.25 times, Delta ~4 times, Omicron ~ 14 times) compared to those receiving Sinopharm's homologous vaccine. No significant changes (P: <0.05) were found in LDH, CPK, CK-MB, ANA, and Anti-CCP levels. However, individuals receiving Sinopharm's booster after two doses showed a significant increase (4 cases) in D-Dimer levels.

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Conclusion: The Razi-CoV-Pars vaccine demonstrates a favorable safety profile and promising potential as an effective booster against current variants, particularly due to its significant protective titer against Omicron.

1. Introduction

Coronavirus Disease 2019 (COVID-19) stands as a major viral disease of this decade, sparking a global pandemic since its emergence in December 2019 in Wuhan City, Hubei Province, China [1]. Initially identified as nCoV-2019 by the Center for Disease Control and Prevention (CDC) in China on January 8, 2020, it was later named COVID-19 (Corona Virus Disease 2019) by the World Health Organization (WHO) [2]. Classified as SARS-CoV-2 by the International Committee on the Classification of Viruses, this virus belongs to the Coronavirus family, known for previous epidemics like Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012, resulting in significant fatalities [3]. In the context of the ongoing pandemic, booster vaccinations are highlighted as a key strategy to reduce COVID-19-related morbidity and mortality [4]. These boosters, widely accessible in numerous countries, are specifically designed to enhance the immune response against emerging variants [5]. and enhance vaccine effectiveness, particularly for vulnerable populations like the immunocompromised and elderly individuals [6,7]. Research underscores the potential waning of immune response to COVID-19 vaccines over time [8,9],necessitating booster doses for increased protection against emerging variants [10].Utilizing heterologous vaccines can further enhance immunity and offer flexibility when the original vaccine doses are unavailable [11]. Ensuring high-quality vaccines and effective immunization practices are vital for successful immunization programs. The primary goal during the COVID-19 pandemic is to shield against severe illness, hospitalization, and fatalities, warranting booster doses if initial protection diminishes over time. The decision on booster doses hinges on factors such as vaccine types, target populations, circulating virus strains, especially variants of concern, and the level of exposure [12]. Amidst global vaccine supply challenges, equitable distribution remains crucial to prioritize high-risk groups across nations.

The National Institute of Allergy and Infectious Diseases (NIAID) is overseeing and providing funding for a study involving adults who have been fully vaccinated against COVID-19 and will receive booster doses of different COVID-19 vaccines. Based on the data obtained from this study, the US Food and Drug Administration has authorized the use of combination booster doses for COVID-19 vaccines. Furthermore, the booster dose of a different vaccine elicited similar or higher antibody responses compared to a booster of the same vaccine [13].

Another crucial aspect to consider regarding the COVID-19 vaccine pertains to its potential side effects. Extensive monitoring has been conducted since the vaccine's introduction and administration to diligently observe the profile of these side effects. Commonly reported reactions after receiving the vaccine consist of diarrhea, nausea, vomiting, localized pain and swelling at the injection site, chills, fatigue, headache, myalgia, arthralgia, and, in rare instances, thrombocytopenia as an adverse effect of the COVID-19 vaccine administration [14]. The results of a study on booster doses in Algeria showed that 74.7 % of the vaccinated population reported at least one local or systemic side effect. These adverse events were more frequent among adenovirus vector vaccines (87.3 %) than inactivated virus vaccines (60.6 %) [5] However, rarer side effects also have been reported, which we discuss below.

The correlation between blood clots and the AZ (AstraZeneca) and J&J (Janssen & Johnson) vaccines has been duly established. [15], According to the European Medicines Agency, 98.5 % of Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) cases are caused by AV vaccination, with ChAdOx1 nCoV-19 and Ad26.COV2.S contributing to 90 and 8.5 % of cases, respectively [16]. As of June 2021, about 21 cases of thrombocytopenia following vaccination Of these, 17 were reported without any previous evidence of thrombocytopenia [14].

Other potential adverse effects include rare occurrences of myocarditis and pericarditis following the administration of booster doses of Pfizer or Moderna vaccines [17,18]. Incidences of potential myocarditis and pericarditis cases have been reported primarily among individuals under the age of 30 [19]. As vaccine programs gradually target younger age groups, which appear to be more susceptible to this potential reaction, pharmacovigilance will be key in estimating its prevalence and providing more accurate information about its risks to the public [20].

A minority of individuals may experience adverse effects following vaccination, including autoimmune syndromes. The primary hypothesis proposed to elucidate the development of such autoimmune syndromes is known as molecular mimicry. According to this hypothesis, the antigens present within the vaccine, as well as the adjuvants employed, possess structural resemblances to self-antigens. The first systematic review of articles on new autoimmune syndromes after the COVID-19 vaccine was published in December 2021. In this study, 276 published cases were identified. The main cases were related to Guillain-Barré syndrome, followed by vaccine-induced thrombotic thrombocytopenia. Less common cases, such as autoimmune liver diseases, immune thrombocytopenic purpura, IgA nephropathy, autoimmune polyarthritis, rheumatoid arthritis, Graves' disease, or systemic lupus erythematosus were also reported [21]. Therefore, it seems necessary to evaluate vaccines in terms of autoimmune markers.

Razi-Cov-Pars is a SARS CoV-2 combined intramuscular/intranasal recombinant spike protein vaccine that includes two injections at days 0 and 21 followed by an intranasal dose at day 51. It contains a mixture of S1 and S2 protein subunits beside a trimeric S protein formulated and delivered with a plant oil in water adjuvant, Razi Adjuvant System-01 (RAS-01) [22].

Here, our focus is on the utilization of protein-based vaccines as heterologous boosters for inactivated COVID-19 vaccines. These boosters were administered to individuals participating in the clinical study of the Razi-CoV-Pars vaccine, who had previously received two doses of Sinopharm vaccines.

Our objective is to provide a concise summary of findings from recent studies identified through a targeted literature review,

specifically focusing on the evaluation of the recombinant protein subunit booster vaccine, Razi-CoV-Pars, against COVID-19. This study aims to guide future vaccine decisions in regions that have predominantly relied on non-mRNA vaccines for primary doses and are now considering protein-based options for upcoming seasonal vaccination campaigns. Given the urgent need for data to inform policy-making, we will assess the safety and immunogenicity of Razi-CoV-Pars in adults aged 18 years and older, following the administration of a two-dose inactivated vaccine (Sinopharm). The insights gained from this research could significantly enhance public health strategies and improve protection against emerging variants of SARS-CoV-2.

2. Methods

2.1. Study design and participants

This study was designed for more detailed investigation of the booster phase of Razi-CoV-Pars vaccine, which is a double blinded clinical trial to access safety and immunogenicity of recombinant protein subunit vaccine.

The participants in this study received two different vaccine platforms, including Sinopharm inactivated virus vaccine (BBIBP-CorV) and Razi-CoV-Pars vaccine (recombinant protein-based vaccine in Iran based on SARS-CoV-2 recombinant protein including S1 and S2 monomers and S-trimer formulation received oil in water adjuvant system RAS-01) as a booster dose.

These participants were divided into two groups to receive the booster dose: the first group who received two doses of Sinopharm/BBIBP-CorV vaccine between 3 and 6 months ago, Sinopharm's inactivated virus vaccine platform was prescribed again as a booster dose.

The second group received the Razi-CoV-Pars vaccine 3 or 6 months after the administration of two doses of the Sinopharm/BBIBP-CorV (Fig. 1).

All participants were required to have no or well-controlled comorbidities. Key exclusion criteria were previous SARS-CoV-2 infection, history of anaphylaxis, history of allergy to a vaccine ingredient, pregnancy, breastfeeding, intent to conceive, and current use of anticoagulants. Full details of the inclusion and exclusion criteria can be found in the Supplementary Methods [23].

2.2. Ethics approval and consent to participate

This study was registered with the Iranian Registry of Clinical Trial at www.irct.ir, IRCT20201214049709N4. Registered November 29, 2021 [23].

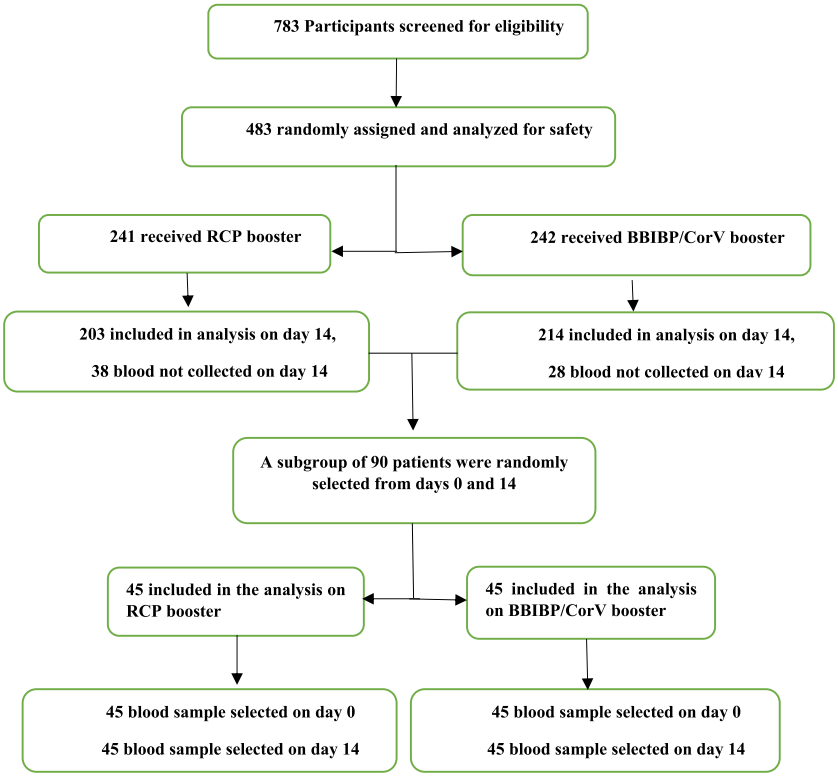

Fig. 1. Participant flow diagram

2.3. Data collection

After vaccination, all participants were monitored for 30 min for immediate adverse reactions and were trained to record all adverse events occurring within 7 days after injection on diary cards. Adverse events occurring 8–30 days later were recorded in contact cards. Throughout the trial, participants were requested to record all serious adverse events and pregnancy outcomes. The causal association between vaccination and adverse events was determined by the trained investigators.

Serum samples were collected to evaluate neutralizing activity against variants of SARS-CoV-2 before vaccination (Day 0) and on Day 14 post-vaccination for all participants.

2.4. Biochemical study

At this stage, the serum of people who received the booster vaccine dose with different platforms were examined for 3 cardiac markers including CPK, LDH and CK-MB by commercial kits made by the Delta Darman Co. with catalogue number CPK(PI026), LDH (PI021) and CK-MB(CK-MB-LQ). Biochemical tests were performed with strict quality control with high accuracy, precision and repeatability.

2.5. Autoimmune investigation

In this section, sera were examined for immune markers by commercial kits made by the Diametera Co. with catalogue number ANA (DKO099) and Anti-CP (DKO149). Immunological markers were measured by ELISA method.

2.6. Coagulation test

In this section, we checked the D-Dimer (Cat number:11–603) test for the presence of thrombosis. This test was performed using citrated plasma collected from the people participated in booster phase of Razi-CoV-Pars. The method was semi-quantitative based on agglutination.

2.7. Measuring the amount of antibodies in the serum against VOC

In this section, a kit was designed using the indirect ELISA method, which was used to measure the antibodies in the serum of people receiving a booster dose. The designed method was checked and validated by positive and negative control sera several times to measure the accuracy and repeatability of this method. And finally sera were examined for the presence of antibodies against protein spikes of Wuhan, Delta and O. micron.

We designed an indirect ELISA method using the spike protein of different variants, which was diluted with carbonate-bicarbonate buffer, and then we coated the spike protein in the high binding wells, the blocking was performed using Skim Milk, and an indirect ELISA method was designed to measure the antibody. Finally, we did and tested the serum of people with different dilutions [22].

3. Results

3.1. Investigating the immunogenicity of the booster dose of Razi-CoV-Pars and Sinopharm vaccines against different variants

The antibody titer on day zero was very low ($\sim< 5 \times 10^{4}$) in all participant before the booster dose injection. In the next step, after the injection of the booster dose, the antibody titer was measured against different variants in the people who received the booster dose

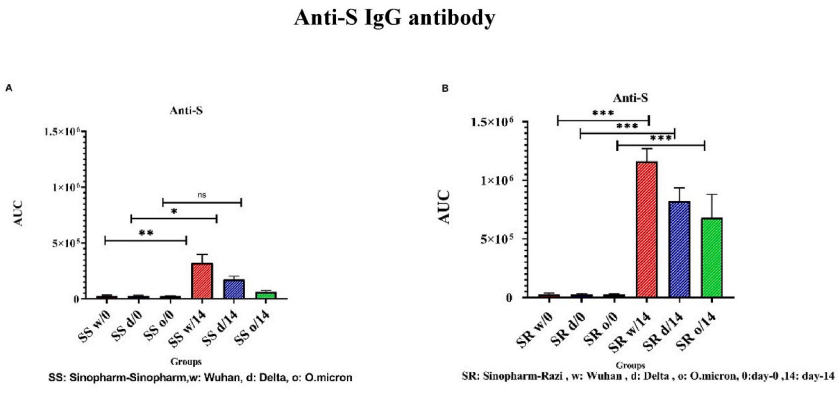

Fig. 2. A) Anti-S IgG antibody responses 14 days after vaccination with the sinopharm/BBIBP- CorV.COVID-19 vaccine, B) Anti-S IgG antibody responses 14 days after vaccination with the RCP.COVID-19 vaccine

of Sinopharm/BBIBP-CorV and Razi-CoV-Pars ($\sim 1.3 \times 10^6$) vaccines.

What was obtained from our results, the people who received the Sinopharm/BBIBP-CorV booster dose who received before two doses of Sinopharm/BBIBP-CorV showed a noticeable change in their antibody titer against the Wuhan ($\sim 4 \times 10^5$) and it also showed a slight increase against the Delta ($\sim 2 \times 10^5$) But the changes of antibody titer against the O. micron ($\sim 5 \times 10^4$) variant did not show a noticeable increase.

In participant who received the booster dose of Razi-CoV-Pars vaccine on the Sinopharm/BBIBP-CorV vaccine, against Wuhan, a significant increase in antibody titer ($\sim 1.3 \times 10^6$) was observed, these changes were about 26 times more than the initial antibody titer before the booster dose was injected. Also, the changes in antibody titer against the Delta ($\sim 0.8 \times 10^6$) increased significantly, but it showed a slight decrease compared to the Wuhan.

Antibody titer in the sera against the O. micron ($\sim 0.7 \times 10^6$(also increased significantly, but compared to the previous two variants, this titer also showed a slight decrease (Fig. 2).

3.2. Biochemical results

3.2.1. Lactate Dehydrogenase (LDH), Creatine Phospho Kinase(CPK) and CK-MB levels

The investigations did not reveal any significant increase in serum LDH, CPK, and CK-MB levels among the groups that received booster doses of Razi-CoV-Pars vaccine and Sinopharm/BBIBP-CorV. However, in the group that received Sinopharm/BBIBP-CorV as a booster dose after two doses of Sinopharm vaccine, there was a slight increase compared to the other groups. This increase, however, was not statistically significant (Fig. 3).

3.3. Autoimmune investigation results

3.3.1. Examining anti-Nuclear Antibody(ANA) levels and anti CCP (anti-cyclic citrullinated peptide) by ELISA method

No significant changes were observed in the serum tests related to autoimmune factors in any of the groups. However, the average in the group that received a booster dose of the Sinopharm/BBIBP-CorV vaccine, after receiving two doses of the Sinopharm primary vaccine was higher than in the other group (Fig. 4).

3.4. Coagulation test results

3.4.1. Measurement of D-Dimer by agglutination method

The measurement of the D-Dimer test using citrated plasma was conducted on individuals from various groups. The results indicated that there were no notable changes in the groups that received the Razi-CoV-Pars booster vaccine who before received the Sinopharm/BBIBP-CorV primary vaccine. However, a significant increase in D-Dimer levels was observed in individuals who received Sinopharm's booster vaccine in comparison to those who received Sinopharm's primary vaccine (Fig. 5).

4. Discussion

This research was designed to investigate the humoral immunogenicity of the Razi-CoV-Pars vaccine against the SARS-CoV-2 virus using the ELISA method. The chosen method for evaluating the antibodies at the Razi Institute was the indirect ELISA method. Previous studies have shown that; the ELISA method is simple, sensitive, relatively inexpensive and requires a small amount of serum. Furthermore, it provides us with quantitative and qualitative results and can be modified and used as needed.

A study conducted in the UAE in 2022 This observational-blind, randomized, controlled phase 3 study in adults over 18 years of age to evaluate the safety and immunogenicity of NVX-CoV2373 as a heterologous booster compared with BBIBP-CorV which is used as a

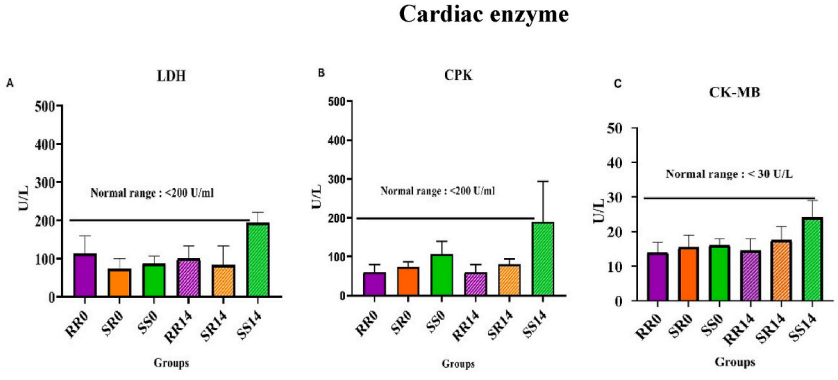

Fig. 3. A) Changes in LDH enzyme, B) Changes in CPK enzyme, C) Changes in CK-MB enzyme, 14 days after vaccination with the RCP and sinopharm/BBIBP-CorV.COVID-19 vaccine.

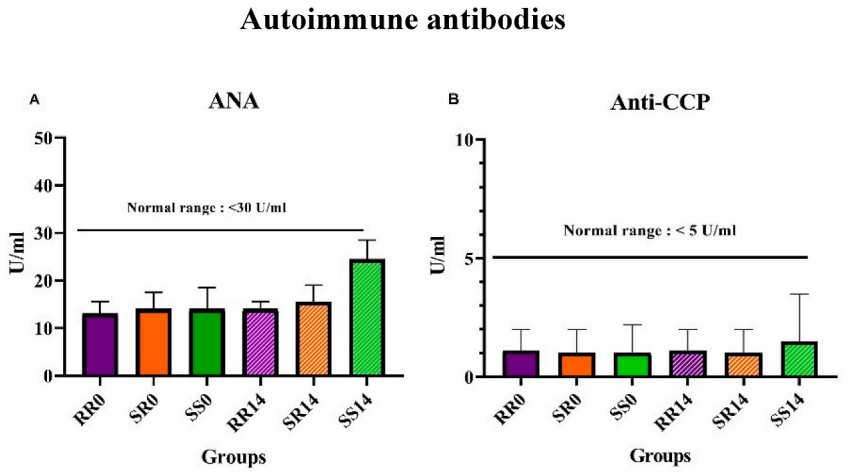

Fig. 4. A) Changes in ANA, B) Changes in Anti-CCP, 14 days after vaccination with the RCP and sinopharm/BBIBP-CorV.COVID-19 vaccine.

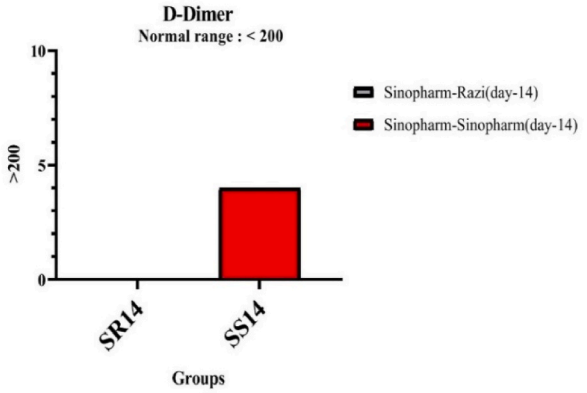

Fig. 5. Changes in D-Dimer 14 days after vaccination with the RCP and sinopharm/BBIBP-CorV.COVID-19 vaccine.

homologous enhancer, was performed. For this interim analysis, anti-spike IgG and neutralizing antibodies against SARS-CoV-2 were measured at baseline, day 14, and day 28. Finally, immunogenicity by anti-spike (anti-S) IgG and antibodies was measured. Neutralization against SARS-CoV-2 to the ancestral strain (Wuhan) was evaluated on days 0, 14, 28 and 180. This study met its primary endpoint and also demonstrated statistically higher neutralization responses of approximately 6-fold when NVX-CoV2373 was used as a heterologous enhancer compared to BBIBP-CorV as a homologous enhancer [24].

In this study, the humoral immunogenicity of the vaccination was assessed against three variants: Wuhan, Delta and O. micron. In each case, the Razi-CoV-Pars vaccine demonstrated high immunogenicity when administered as a heterologous booster dose compared to when each of these vaccines was received as a homologous booster dose.

Another study that was conducted in Iran at Pasteur Institute, this study aimed to evaluate and compare PastoCovac Plus protein subunit vaccine in parallel with ChAdOx1-S (AstraZeneca) and BBIBP-CorV (Sinopharm) in primary volunteers vaccinated with two doses of ChAdOx1-S or BBIBP-CorV was performed.

The use of PastoCovac Plus booster in primary subjects with BBIBP-CorV or ChAdOx1-S successfully increased the levels of specific antibodies without any serious side effects [25].

In our study, according to the antibody titer assays against Wuhan, Delta, and O. micron variants, the BBIBP-CorV/RCP group (*P-value* < 0.05) increased (Wuhan: $\sim 1.3 \times 10^6$, Delta: $\sim 0.8 \times 10^6$, O.micron: $\sim 0.7 \times 10^6$) in the anti-spike IgG titer compared to the BBIBP-CorV/BBIBP-CorV (Wuhan: $\sim 4 \times 10^5$, Delta: $\sim 2 \times 10^5$, O.micron: $\sim 5 \times 10^4$) group (*P- value* > 0.05). It showed a significant difference between the two groups in terms of increasing neutralizing antibodies.

Another study in Iran showed that after PastoCovac booster dose, significant increases were observed against Wuhan ($P < 0.001$) and Omicron variant ($P < 0.01$) compared to homologous BBIBP-CorV regimen [26] as we observed in our study.

A systematic review was conducted in PubMed for English case reports and case series studies and finally 100 studies were included. The aim of this study was to compare the cardiac complications of the COVID-19 vaccine based on the type of vaccine (mRNA, vector-based, and inactivated vaccine). Myocarditis (with an overall rate of about 1.62 %) was shown to be the most common

cardiac event after COVID-19 immunization. More than 90 % of post-vaccination COVID-19 myocarditis occurred after receiving mRNA vaccines (Moderna & Pfizer-BioNTech), but this event was less frequently reported for viral vector-based and inactivated vaccines. Myocarditis has been reported more often in men and after the second dose of immunization [27].

Although such studies about recombinant protein vaccines to best of our knowledge are very scarce or may not have been conducted, we evaluated the cardiac and coagulation markers of the two vaccines and compared them. We did not find any significant increase in cardiac markers after the administration of the Razi-CoV-Pars and Sinopharm/BBIBP-CorV vaccines as booster doses. However, the average level of cardiac enzymes in the groups that received a homologous booster dose of Sinopharm/BBIBP-CorV (LDH: ~200 U/ml, CPK: ~200 U/ml, CK-MB: ~25 U/L) was higher than the group that received a heterologous and homologous booster dose of the Razi-CoV-Pars (LDH: ~ <100 U/ml, CPK: ~ <100 U/ml, CK-MB: ~ <20 U/L) vaccine. (Normal range: LDH: <200 U/ml, CPK: <200 U/ml, CK-MB: <30 U/L)

There was no increase in D-Dimer in the group that received the Razi-CoV-Pars vaccine, but we did observe a significant increase (4 cases: >200) in the group that received Sinopharm/BBIBP-CorV. However, further investigation is required in this case as our community sample size was small, and therefore, we cannot draw a definitive conclusion.

A comprehensive analysis of the emergence of rare autoimmune diseases after COVID-19 vaccination was performed by Guo et al. [28] based on a systematic search of PubMed to identify relevant literature on COVID-19 vaccination and new autoimmune phenomena published up to February 1, 2023. Growing evidence suggests that COVID-19 vaccination may cause new autoimmune diseases, including autoimmune glomerulonephritis, autoimmune rheumatic diseases.

In this study, we also evaluated some auto-immune markers of immunity or the occurrence of unwanted side effects caused by the Razi-CoV-Pars and Sinopharm/BBIBP-CorV vaccines. According to our evaluations, there was no significant increase in autoantibodies in the mentioned vaccines. However, the average titer of these autoantibodies was higher in the group that received a homologous booster dose of the Sinopharm/BBIBP-CorV vaccine (Anti-CCP: ~1.5 U/ml, ANA: ~25 U/ml) compared to other groups (Anti-CCP: ~ <1.0 U/ml, ANA: ~ <20 U/ml). (Noermal range: Anti-CCP: <5.0 U/ml, ANA: <30 U/ml)

The optimal strategy for maintaining protective immunity against SARS-CoV-2 amid evolving variants is a critical issue that requires thorough investigation [29].Recent clinical data sheds light on the pros and cons of protein-based and inactivated whole virus vaccines as booster platforms. However, significant questions persist concerning safety and long-term immune responses [30].A relevant study compared the Razi-Cov-Pars recombinant protein vaccine to the inactivated virus vaccine Sinopharm as heterologous boosters for individuals initially vaccinated with Sinopharm. Both were deemed safe based on standard biochemical and immunological measures taken 4 weeks post-boost. Nevertheless, the Sinopharm booster triggered a slight yet statistically notable rise in certain coagulation markers like D-dimer and fibrinogen within normal levels. While the clinical implications are uncertain, any changes induced by boosters necessitate careful interpretation and further investigation to comprehensively assess safety profiles. Besides safety, the selection of an optimal booster platform influences vaccine efficacy against emerging variants. This study revealed that Razi-Cov-Pars resulted in a lesser decrease in neutralizing antibody levels against Omicron and Delta sublineages compared to Sinopharm boosting. Structurally, Razi-Cov-Pars includes the conserved S2 subunit domain, potentially enabling cross-recognition of epitopes preserved across variants. In contrast, inactivated whole virus vaccines present the entire spike protein but rely more on previously induced epitopes that can mutate [23,31].

Mechanistically, protein-based vaccines like Razi-Cov-Pars may also stimulate qualitatively different immune responses through activation of both B and T cells. The oil-based adjuvants in Razi Cov Pars induce systemic immune activation including cellular immunity. B cells produce neutralizing antibodies while T cells maintain immunological memory and support rapid clearance of reinfection through recognition of infected cells. This diversity in immune targets could confer advantages for cross-protection that warrant deeper investigation [23,32]. While boosting aims to increase immunity, long-term effects on the immune response remain uncertain. Factors like antibody persistence over 6–12 months, the durability of immune memory, and the longevity of any changes to cellular immunity profiles require extensive follow-up [33]. Here is one way to phrase it in an English paragraph: Extensive clinical studies of the Razi-Cov-Pars protein-based vaccine, which have been published in several peer-reviewed journal articles, have provided insights into its long-term immune effects compared to inactivated whole virus vaccines. Longitudinal monitoring reported in these publications shows that Razi-Cov-Pars elicits significantly better sustained markers of immunity based on clinical and laboratory monitoring over prolonged periods, as assessed by metrics such as neutralizing antibody levels, B and T cell memory responses, and other immune parameters. A notable preservation and durability of protective immunity has been observed when boosting with Razi Cov Pars relative to inactivated vaccines, with differences reported of multiple fold over several months [22,23,32].

5. Conclusion

The study emphasizes the potential of the Razi-CoV-Pars vaccine as a booster against COVID-19 variants, especially Omicron. It significantly increases antibody levels compared to homologous vaccination. Participants who received the Razi-CoV-Pars booster showed a notable rise in antibodies against various variants of concern, indicating the vaccine's ability to enhance immune responses in those previously vaccinated with the Sinopharm vaccine. This suggests that using different vaccines for boosting could be a viable strategy in addressing the changing landscape of COVID-19. Additionally, the favorable safety profile observed among participants is promising, suggesting that the Razi-CoV-Pars vaccine can be administered with minimal risk of severe adverse effects. However, it's important to note the study's limitations, such as the relatively small sample size and the lack of long-term data, which could impact result reliability. Therefore, further research with larger cohorts and extended follow-up periods is crucial to fully understand the efficacy and safety of the Razi-CoV-Pars vaccine in diverse populations and its role in future vaccination strategies against COVID-19.

Role of funding source

The study is funded by the Razi Vaccine and Serum Research Institute. The study's sponsor helped with the design and performed the immunogenicity tests, but it was blinded to the identity of the participants in all blood specimens.

CRediT authorship contribution statement

Esmat Malek: Writing – original draft, Supervision, Investigation, Conceptualization. **Mohammad Hossein Fallah Mehrabadi:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Ali Es-haghi:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Mojtaba Nofeli:** Writing – review & editing, Validation, Supervision, Resources, Project administration. **Ali RezAli Rezae Mokaram:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Monireh Haji Moradi:** Validation, Data curation. **Seyad Hossein Razaz:** Validation, Investigation, Data curation. **Masoud Solaymani-Dodaran:** Supervision, Investigation, Formal analysis, Conceptualization. **Saeed Kalantari:** Writing – review & editing, Validation, Supervision, Resources, Project administration. **Fariba Sadeghi:** Writing – review & editing, Validation, Supervision, Project administration. **Ladan Mokhberalsafa:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Seyed Reza Banihashemi:** Writing – review & editing, Project administration, Methodology, Conceptualization.

Data and code availability statements

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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